

Retrospective Family Study of Childhood Medulloblastoma

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Medulloblastoma is the most common malignant central nervous system tumor of childhood and can occur sporadically or in association with inherited cancer susceptibility syndromes such as the nevoid basal cell carcinoma syndrome (NBCCS). To determine whether an association existed between the risk of developing medulloblastoma and undiagnosed syndromes, we retrospectively reviewed clinical data on 33 patients with medulloblastoma from a single institution and compared them with their unaffected relatives (n = 46). Six patients had tumors showing desmoplastic histology. Two of the six met diagnostic criteria for NBCCS. One NBCCS patient had a missense mutation of patched-1 (PTCH1); the other had no identifiable PTCH1 mutation. Two patients with isolated desmoplastic medulloblastoma had an insertion and splice site mutation, respectively, in suppressor of fused (SUFU). All patients with nondesmoplastic medulloblastoma histology received molecular testing for SUFU. None of these patients had an identifiable mutation in PTCH1 or SUFU. We performed a clinical evaluation for Greig cephalopolysyndactyly syndrome (GCPs) in four medulloblastoma families, who exhibited macrocephaly as the only finding consistent with the diagnosis of GCPs. Molecular analysis of GLI3 in these four families was negative. There was a paucity of clinical findings among the majority of medulloblastoma patients in this study group to suggest a definable cancer genetic syndrome. We conclude that clinically recognizable syndromes are uncommon among patients with medulloblastoma, however, PTCH1 and SUFU mutations are present at a low but significant frequency.

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KEY WORDS: medulloblastoma; PTCH1; SUFU; GLI3

INTRODUCTION

Medulloblastoma (MB) is a primitive neuroectodermal tumor (PNET). It commonly arises in the cerebellum and can spread throughout the central nervous system and metastasize systemically. Three major MB histologic types are classic, desmoplastic, and large-cell variant (Table I). Classic MB is the most common. Desmoplastic MB is associated with inactivation of PTCH1 and found in 15% of pediatric cases. Large-cell MB is rare and associated with amplification of MYC.

The incidence of MB in the US is 1.5–2 cases per 100,000, producing approximately 350 new cases per year and has a median age of onset of 9 years. There is a higher incidence (1.5:1) and poorer prognosis in males than females. Most cases are sporadic, however, mutations of genes in the sonic hedgehog (SHH) pathway and WNT/wingless pathway have been shown to occur in a small portion of MB [Ellison, 2002]. Mutations of PTCH1, APC, and SUFU are found in both germline and somatic forms [Ellison, 2002]. Mutations of PTCH2, SMOH, CTNNB1, and AXIN1 have been found in the somatic state [Ellison, 2002]. Several syndromes have an increased incidence of MB including NBCCS (MIM 109400) and Turcot syndrome [MIM 276300; Ellison, 2002]. We performed a retrospective analysis to determine if radiographic abnormalities (affected n = 56) and physical findings (affected n = 31) from MB patients diagnosed at a single institution from 1969 to 1997 to confirm the above data and determine if other unrecognized syndrome(s) was present in children with MB.

METHODS

Patients with MB diagnosed at Children's National Medical Center (CNMC) in Washington, DC from 1969 to 1997 were identified (n = 88). The median age at diagnosis was 69 months (range 3–273 months). A majority of children (69%) presented with symptoms of increased intracranial pressure (i.e., morning headache, nausea, vomiting, irritability, and lethargy) with a mean duration of 1.6 months to time of diagnosis. The survival rate was 50% at 5 years and 52% at 10 years [Stavrou et al., 2001]. To be eligible for the current study, patients had to be locatable, and willing to be clinically evaluated. Thirty-three patients fulfilled these criteria (n = 33, 21 males, 12 females). Reasons for non-participation included refusal to participate (n = 15), non-traceable (n = 1), or deceased (n = 39). Parents (n = 46, 19 males, 27 females) of the participating MB patients were examined. Informed consent was obtained from subjects, parents, and/or guardians under institutional review board approved protocols from National Cancer Institute and CNMC.

Among the 33 cases reviewed, 2 patients met diagnostic criteria for NBCCS with jaw cysts, palmar/plantar pits, and calcification of the falx cerebri. If a patient was diagnosed with

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TABLE I. Histopathologic Types of Medulloblastoma

Medulloblastoma type	Histology	Immunostaining
Classic	Small round cells with hyperchromatic nuclei, scant cytoplasm, and high mitotic index	Vimentin, Synaptophysin
Desmoplastic	Nodular regions of high cellularity and high mitotic rate with reticulin fiber surrounding reticulin free areas with low mitotic rate	Neuron specific enolase, Synaptophysin, Neurofilaments
Large cell	Tumor cells with large nuclei, prominent nucleoli, abundant cytoplasm, high mitotic index with increased apoptosis, and necrosis	Vimentin, Synaptophysin

NBCCS, all available first degree relatives were examined to determine their affection status. These 2 NBCCS cases and their relatives were evaluated separately leaving a total of 31 affected (19 males, 12 females) and 41 unaffected (16 males, 25 females) participants for clinical analyses.

Physical features were evaluated in patients and compared with their parents (Table II). Physical measurements of affected subjects and their unaffected relatives were normalized for age and compared with population normograms [Hall et al., 1995]. Measurements that exceeded two standard deviations from the mean were scored as abnormal. Macrocephaly relative to height was determined by the formula of Bale et al. [1991]. Adult obesity was determined using body mass index (BMI) formula. Obesity for children (BMI > 95th centile) was determined using Centers for Disease Control age and sex specific BMI charts.

Screening for germline PTCH1 and SUFU mutations was performed on a subset of MB patients. DNA from patients with desmoplastic histology (n = 6) or previous molecular evidence of 9q loss of heterozygosity (LOH) [Vortmeyer et al., 1999] were analyzed (total patients combined n = 11) for both

PTCH1 and SUFU mutations. An additional 22 patients with available lymphocyte derived germline DNA were analyzed solely for SUFU mutations. The coding exons of GLI3, PTCH1, and SUFU were amplified from genomic DNA by standard methods. Bi-directional dye-terminator sequencing was used for mutation analysis. PCR conditions and primer sequences are available upon request.

Plain radiographs and/or CT films were available on 56 MB patients (32 males, 24 females). Thirty-one of these patients were also in the clinical portion of the study. The remaining 25 patients did not participate in the clinical study due to refusal (n = 14), being untraceable (n = 1) or deceased (n = 10). Radiographs of affected patients and their unaffected relatives (n = 37, 15 males, 22 females) were evaluated for evidence of abnormal ribs, hand bones, and spina bifida occulta.

Frequencies of clinical features were determined. Cross-tabulation analysis of the variables of interest among affected and unaffected groups in each clinical/radiologic category was performed. Statistical significance was calculated using non-parametric analyses with Fisher's exact test from StatXact-4

TABLE II. Frequency of Clinical Signs in Affected Individuals With Medulloblastoma and Their Unaffected Relatives

Clinical signs	Affected (%)	Unaffected (%)	P
Short stature <2 SD	12/31 (31)	2/41 (5)	<0.01
Under weight <2 SD	2/31 (6)	0/41 (0)	0.18
Obesity >2 SD	4/31 (13)	8/41 (20)	0.53
Microcephaly <2 SD	4/31 (13)	0/41 (0)	0.03
Macrocephaly >2 SD	0/31 (0)	4/41 (10)	0.10
Short lower segment <2 SD	19/31 (61)	3/41 (7)	<0.01
Inner canthal distance <2 SD	6/31 (19)	2/41 (5)	0.05
Inner canthal distance >2 SD	1/31 (3)	3/41 (7)	0.32
Interpupillary distance <2 SD	3/31 (10)	1/41 (2)	0.18
Interpupillary distance >2 SD	1/31 (3)	3/41 (7)	0.32
Outer canthal distance >2 SD	25/31 (81)	24/41 (59)	0.03
Right middle finger <2 SD	4/31 (13)	1/41 (2)	0.09
Right middle finger >2 SD	0/31 (0)	6/41 (15)	0.03
Left middle finger <2 SD	6/31 (19)	2/41 (5)	0.05
Left middle finger >2 SD	0/31 (0)	8/41 (20)	<0.01
Right hand length <2 SD	5/31 (16)	0/41 (0)	0.04
Right hand length >2 SD	1/31 (3)	0/41 (0)	0.43
Left hand length <2 SD	5/31 (16)	1/41 (2)	0.04
Left hand length >2 SD	1/31 (3)	4/41 (10)	0.22
Frontal bossing	3/31 (10)	0/41 (0)	0.08
Abnormal skull shape	3/31 (10)	0/41 (0)	0.08
Strabismus	2/31 (6)	1/41 (2)	0.32
Synophrys	1/31 (3)	0/41 (0)	0.43
Abnormal palate	11/31 (35)	6/41 (15)	0.03
Abnormal teeth	4/31 (13)	2/41 (5)	0.17
Coarse facies	1/31 (3)	0/41 (0)	0.43
Delayed tanner stage	2/31 (6)	0/41 (0)	0.18
Pectus excavatum	10/31 (32)	11/41 (27)	0.18
Clinical scoliosis	4/31 (13)	4/41 (10)	0.27
Metacarpal sign	3/31 (10)	4/41 (10)	0.31
2-3 toe syndactyly	2/31 (6)	2/41 (5)	0.37

v4.01 software package (Cytel Corp., Cambridge, MA). All tests were two-sided.

RESULTS

Identification of NBCCS Patients

Clinical features of NBCCS case 1 (subject ID 2, Table III) were previously reported by Korczak et al. [1997]. We present additional molecular data on this patient. Briefly, the proband is an African American male who developed ataxia at 18 months of age. At 2 years, he developed hydrocephalus and a midline posterior fossa mass was resected and diagnosed as a desmoplastic MB. At age of 5.75 years, he was diagnosed with NBCCS, based on findings of odontogenic keratocysts and multiple basal cell carcinomas in the neck, shoulders, and back where he previously received radiation therapy for MB. Sequencing PTCH1 revealed a germline missense mutation c.1513G > C (G509R). Molecular analysis of SUFU revealed no coding or splice site mutations.

NBCCS case 2 (Table III, ID 25, Fig. 1) is an African American male diagnosed with MB at age of 2 years. He developed numerous basal cell carcinomas in the radiation field at the age of 3 years. Physical examination at the time revealed apparent macrocephaly and hypertelorism, high arched palate, and palmar/plantar pits with radiographic findings of calcified falx and tentorium cerebelli consistent with the diagnosis of NBCCS. His older brother and mother had NBCCS; both exhibited apparent macrocephaly and hypertelorism, palmar/plantar pits, and radiographic abnorm-

alities of spina bifida occulta, scoliosis, calcified falx (older brother only), and calcified falx and tentorium cerebelli (mother only). A younger brother had radiographic findings of metacarpal sign and calcified falx suggesting NBCCS (Fig. 1). Sequencing of lymphocyte derived DNA failed to identify a mutation in the coding exons or splice sites of PTCH1 or SUFU.

Molecular Analysis of PTCH1 and SUFU

Sequencing of PTCH1 on lymphocyte DNA derived from six patients with desmoplastic MB and five patients with 9q LOH and non-desmoplastic histology revealed no coding or splice site mutations (Table III).

SUFU mutation testing was performed on lymphocyte derived DNA from a total of 33 patients. Ten of these patients were previously evaluated (marked by asterisk, Table III) including two patients with isolated MB and desmoplastic phenotype who tested positive for SUFU mutations [Taylor et al., 2002]. All other patients evaluated tested negative (Table III). SUFU case 1 had a splice acceptor mutation in intron 1 (IVS1-1A>T). SUFU case 2 had an adenine insertion at nucleotide position 143 in exon 1 (c.143insA) of SUFU. SUFU cases 1 and 2 did not have any physical abnormalities on examination.

Physical Characteristics

Table II shows the frequencies of physical characteristics for MB patients (affected) and their parents (controls). Short

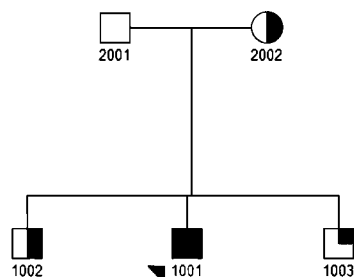
TABLE III. Summary of Molecular Studies of PTCH1, SUFU on Medulloblastoma Patients

Subject ID	Histology	PTCH1	SUFU	Diagnosis
2	Desmoplastic	c.1513G>C	Negative	NBCCS medulloblastoma
5		Np	Negative	Sporadic medulloblastoma
8		Np	Negative	Sporadic medulloblastoma
11		Np	Negative	Sporadic medulloblastoma
14		Np	Negative	Sporadic medulloblastoma
17		Np	Negative	Sporadic medulloblastoma
20		Np	Negative	Sporadic medulloblastoma
22		Negative	Negative	Sporadic medulloblastoma
25*		Negative	Negative	NBCCS medulloblastoma
29*		Negative	Negative	Sporadic medulloblastoma
32	Desmoplastic	Np	Negative	Sporadic medulloblastoma
34		Np	Negative	Sporadic medulloblastoma
37*		Negative	c.143insA	SUFU medulloblastoma
39		Np	Negative	Sporadic medulloblastoma
40		Np	Negative	Sporadic medulloblastoma
41*		Negative	IVS1-1A>T	SUFU medulloblastoma
42*		Negative	Negative	Sporadic medulloblastoma
45*		Negative	Negative	Sporadic medulloblastoma
48		Np	Negative	Sporadic medulloblastoma
50		Np	Negative	Sporadic medulloblastoma
53	Desmoplastic	Np	Negative	Sporadic medulloblastoma
55		Np	Negative	Sporadic medulloblastoma
56*		Negative	Negative	Sporadic medulloblastoma
58		Np	Negative	Sporadic medulloblastoma
60		Np	Negative	Sporadic medulloblastoma
65		Np	Negative	Sporadic medulloblastoma
69		Np	Negative	Sporadic medulloblastoma
70		Np	Negative	Sporadic medulloblastoma
73		Np	Negative	Sporadic medulloblastoma
75*		Negative	Negative	Sporadic medulloblastoma
78	Desmoplastic	Np	Negative	Sporadic medulloblastoma
81		Np	Negative	Sporadic medulloblastoma
82*		Negative	Negative	Sporadic medulloblastoma

Np, not performed.

PTCH1 testing in sporadic medulloblastoma patients were performed under contract with GeneDx, Inc.

A subset of SUFU results (10/33) were previously published by Taylor et al. [2002] (marked by an asterisk).



- NBCCS = Medulloblastoma, macrocephaly, hypertelorism, palmar/plantar pits, calcified falx
- ◼ NBCCS = Macrocephaly, hypertelorism, palmar/plantar pits, calcified falx
- ◻ NBCCS = Metacarpal sign, calcified falx

Fig. 1. Pedigree of NBCCS case 2. NBCCS case 2 has no identifiable germline mutation of *PTCH1* or *SUFU*.

stature and disproportionally shortened lower segment were more prevalent in the MB patient group ($P < 0.01$) compared to the control group. The frequency of short left middle finger was elevated among affecteds ($P = 0.05$) compared with controls. High arched palate (71%) was increased in affected patients compared with controls ($P = 0.03$). Occipito-frontal-circumference (OFC) was within normal limits for the majority of MB patients. Microcephaly was observed in four patients (OFC 50.5 cm/age 10.67 years, OFC 52 cm/age 19 years, OFC 43.9 cm/age 15.67 years, OFC 52 cm/age 24 years), but not in unaffected controls ($P = 0.03$, Table II). Macrocephaly was found in 10% of parents ($n = 3$ males: OFC 60.5 cm, 61 cm, 60 cm and 1 female: OFC 57.5 cm) even after adjustment of OFC for height using the regression formula of Bale et al. [1991]. The three fathers with macrocephaly were Caucasian, the mother was Hispanic. Affected children from these four families were normocephalic. We hypothesized that the occurrence of macrocephaly in these four families was not due to chance alone and evaluated the parents and affected children for a *GLI3* mutation [Erez et al., 2002]. No mutations were found in the coding exons or splice junctions of *GLI3*.

Of the four families, one was available for repeat physical evaluation. Family no. 20 was of Peruvian descent. The proband was diagnosed with MB at 9 years-of-age. At physical examination the mother had macrocephaly (OFC 57 cm), ocular hypertelorism, telecanthus (interpupillary distance [IPD] 6.7 cm, inner canthal distance [ICD] 4.0 cm), broad nasal root, low nasal bridge, and a flat philtrum. The proband was normocephalic (OFC 57.8 cm/age 30 years) with telecanthus (ICD 3.8 cm) and a broad nasal root. Neither patient had physical or radiographic findings suggestive of GCPS.

Radiographic Findings

Table IV shows the radiographic features in MB patients and controls. There was an elevated frequency (13%, $P = 0.03$) of spina bifida occulta (SBO) in the affected group and no detectable radiographic evidence of SBO among controls. No other radiographic features evaluated showed significant differences in patients versus controls.

DISCUSSION

A statistically significant increase in short stature and shortened lower segment was found among MB patients in this series. These findings are consistent with previous studies

TABLE IV. Frequency of Radiographic Signs in Affected Individuals With Medulloblastoma and Their Unaffected Relatives

Radiographic sign	Affected (%)	Unaffected (%)	<i>P</i>
Bifid ribs	1/56 (2)	0/37 (0)	0.60
Spina bifida occulta	7/56 (13)	0/37 (0)	0.03
Scoliosis	3/56 (5)	0/37 (0)	0.21
Short fourth metacarpal	3/56 (5)	0/37 (0)	0.21
Flame shaped lucency hand	2/56 (4)	0/37 (0)	0.36

that have reported a decrease in adult height of children treated with cranial spinal radiation therapy (CSRT) for MB and other childhood brain cancers [Gurney et al., 2003; Xu et al., 2003]. Xu et al. [2003] found that the severity of growth impairment increases with an earlier age of diagnosis and timing of initial CSRT and amount of radiation received. Spinal radiation causes spinal injury and resultant poor response to human growth hormone replacement therapy resulting in disproportional growth. An increased frequency of short left middle finger was present in affected patients compared to their unaffected parents. These data suggest a systemic effect of CSRT on bone growth.

Although four instances of microcephaly (13%) were diagnosed among affected patients, no structural CNS abnormalities were noted. It was not possible to determine the specific etiology (i.e., genetic vs. non-genetic) of microcephaly among these patients. The frequency of abnormal palate was significantly different in MB patients (35%) and their unaffected parents (15%). The majority of patients and controls had a high arched palate. No conclusions were drawn from this non-specific finding.

Three fathers and one mother of MB patients had an OFC greater than two standard deviations above the mean. The three men were Caucasian. The female was Hispanic. The possibility of racial differences accounting for the observed difference in OFC of the woman is possible, given that the regression formula for OFC based on height was derived by Bale et al. [1991] based on a Caucasian population. Given the involvement of *SHH* pathway (*PTCH1*, *SUFU*) in the predisposition to MB, we investigated whether the macrocephaly observed in these families could be an indicator that *GLI3* mutations might predispose to MB in a subset of families. However, no identifiable mutations were found in the coding region or splice sites of *GLI3*.

Radiographic studies found an elevated frequency of SBO among patients compared to their unaffected relatives. The observed 13% frequency was consistent with the 23% prevalence that has been observed in past studies of SBO detected by radiographic study on normal adults [Fidas et al., 1987]. The control group (consisting of adults) had no observed SBO. Over time, both children and adults exhibit progressive closures of SBO defects [Sutow and Pryde, 1956]. It has been hypothesized that the observed steady decrease in SBO prevalence with age is probably due to degenerative calcification filling the defects [Fidas et al., 1987].

The major limitation of this study is that the data were derived from a hospital-based population and thus represents the more severe end of the clinical spectrum of MB patients that are referred to CNMC. This is a single institution study, with limited participation from all eligible families, thus the findings may not be representative of all MB patients.

Our data suggests that in a minority of patients with apparent "sporadic MB," a more detailed evaluation for possible genetic predisposition is warranted. Specifically, dermatologic findings, such as palmar/plantar pits and basal cell carcinomas, dental findings of jaw cysts, and radiographic evidence of

falx calcification suggest a diagnosis of NBCCS [Kimonis et al., 1997]. Individuals with desmoplastic histology and no other associated physical findings should be considered for SUFU mutation analysis. A physician performing a screening intake should perform a family history and physical examination of parents and unaffected siblings with a focus on measuring OFC and inspection of the hands and feet for evidence of preaxial or mixed preaxial and postaxial polydactyly to determine if the evaluation for GCPS or NBCCS should be further investigated. There was a paucity of clinical findings among the majority of MB patients in this study group to suggest a definable cancer genetic syndrome. Thus, the etiology of sporadic nondesmoplastic MB remains undefined.

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